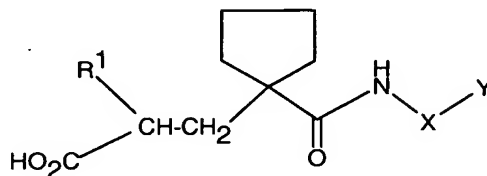


Claims

- 1 A compound of formula (I), a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof;



(I)

5 wherein

R<sup>1</sup> is C<sub>1-6</sub>alkyl which may be substituted by one or more substituents, which may be the same or different, selected from the list: halo, hydroxy, C<sub>1-6</sub>alkoxy, hydroxyc<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxyc<sub>1-6</sub>alkoxy, carbocyclyl, carbocycloxy, C<sub>1-4</sub>alkoxycarbocycloxy, heterocyclyl, heterocycloxy, -NR<sup>2</sup>R<sup>3</sup>, -NR<sup>4</sup>COR<sup>5</sup>, -NR<sup>4</sup>SO<sub>2</sub>R<sup>5</sup>, -CONR<sup>2</sup>R<sup>3</sup>, -S(O)<sub>p</sub>R<sup>6</sup>, -COR<sup>7</sup> and -CO<sub>2</sub>(C<sub>1-4</sub>alkyl); or R<sup>1</sup> is carbocyclyl or heterocyclyl, each of which may be substituted by one or more substituents from said list, which substituents may be the same or different, which list further includes C<sub>1-6</sub>alkyl; or R<sup>1</sup> is hydrogen, C<sub>1-6</sub>alkoxy, -NR<sup>2</sup>R<sup>3</sup> or -NR<sup>4</sup>SO<sub>2</sub>R<sup>5</sup>;

15 wherein

R<sup>2</sup> and R<sup>3</sup>, which may be the same or different, are carbocyclyl or heterocyclyl (each of which may be substituted by C<sub>1-4</sub>alkyl, hydroxy or C<sub>1-4</sub>alkoxy); or are hydrogen or C<sub>1-4</sub>alkyl; or R<sup>2</sup> and R<sup>3</sup> together with the nitrogen to which they are attached form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C<sub>1-4</sub>alkyl)piperazinyl group;

R<sup>4</sup> is hydrogen or C<sub>1-4</sub>alkyl;

R<sup>5</sup> is C<sub>1-4</sub>alkyl, CF<sub>3</sub>, carbocyclyl, C<sub>1-4</sub>alkylcarbocyclyl, C<sub>1-4</sub>alkoxycarbocyclyl, heterocyclyl, C<sub>1-4</sub>alkoxy or -NR<sup>2</sup>R<sup>3</sup>;

R<sup>6</sup> is C<sub>1-4</sub>alkyl, carbocyclyl, heterocyclyl or NR<sup>2</sup>R<sup>3</sup>; and

25 R<sup>7</sup> is C<sub>1-4</sub>alkyl, carbocyclyl or heterocyclyl;

p is 0, 1, 2 or 3;

X is the linkage  $-(CH_2)_n-$  or  $-(CH_2)_q-O-$  (wherein Y is attached to the oxygen); wherein one or more hydrogen atoms in linkage X may be replaced independently by  $C_{1-4}$ alkoxy; hydroxy; hydroxy $C_{1-3}$ alkyl;  $C_{3-7}$ cycloalkyl; carbocyclyl; heterocyclyl; or by  $C_{1-4}$ alkyl optionally substituted by one or more fluoro or phenyl groups; n is 3, 4, 5, 6 or 7; and q is 2, 3, 4, 5 or 6; and

Y is phenyl or pyridyl, each of which may be substituted by one or more groups  $R^8$  which may be the same or different, wherein  $R^8$  is hydroxy; mercapto; halogen; cyano; acyl; amino; mono( $C_{1-4}$ alkyl)amino; di( $C_{1-4}$ alkyl)amino; carbocyclyl or heterocyclyl (either of which is optionally substituted by  $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, halo $C_{1-6}$ alkoxy,  $C_{1-6}$ alkylthio or halogen);  $C_{1-6}$ alkoxy; phenoxy;  $C_{1-6}$ alkylthio; phenylthio; or alkyl optionally substituted by  $C_{1-6}$ alkoxy, halo $C_{1-6}$ alkoxy,  $C_{1-6}$ alkylthio, halogen or phenyl; or

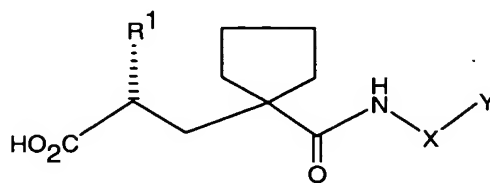
two  $R^8$  groups on adjacent carbon atoms together with the interconnecting carbon atoms may form a fused 5- or 6-membered carbocyclic or heterocyclic ring, optionally substituted by  $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, halo $C_{1-6}$ alkoxy,  $C_{1-6}$ alkylthio, or halogen.

2 A compound according to claim 1, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein  $R^1$  is hydrogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxy $C_{1-3}$ alkyl,  $C_{1-6}$ alkoxy $C_{1-6}$ alkoxy $C_{1-3}$ alkyl or  $C_{1-6}$ alkyl substituted by phenyl.

3 A compound according to claim 2, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein  $R^1$  is hydrogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxy $C_{1-3}$ alkyl or  $C_{1-6}$ alkoxy $C_{1-6}$ alkoxy $C_{1-3}$ alkyl.

4 A compound according to claim 3, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein  $R^1$  is  $C_{1-4}$ alkyl or  $C_{1-6}$ alkoxy $C_{1-3}$ alkyl.

5 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, of formula Ia:



(Ia)

- 6 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof wherein X is  $-(\text{CH}_2)_n-$  and wherein
- 5 one or more hydrogen atoms in linkage X may be replaced by one or more of the groups defined claim 1.
- 7 A compound according to any preceding claim, pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when present n is 3 or 4.
- 10 8 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein  $\text{R}^8$  is  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy, hydroxy, mercapto, halo, cyano, carbocyclyl or heterocyclyl; or two  $\text{R}^8$  groups on adjacent carbon atoms together with the interconnecting carbon atoms may form a fused 5- or 6-membered carbocyclic or heterocyclic ring, optionally
- 15 substituted by  $\text{C}_{1-6}$ alkyl, halo $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy, halo $\text{C}_{1-6}$ alkoxy,  $\text{C}_{1-6}$ alkylthio or halogen.
- 9 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when  $\text{R}^8$  is carbocyclyl,  $\text{R}^8$
- 20 is cyclopentyl, cyclopropyl, cyclohexyl or phenyl.
- 10 A compound according to any one of claims 1 to 8, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when  $\text{R}^8$  is
- 25 heterocyclyl,  $\text{R}^8$  is pyridyl, oxadiazolyl, pyrazolyl or triazolyl.
- 11 A compound according to any one of claim 1 to 8, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when Y is phenyl and two  $\text{R}^8$  groups on adjacent carbon atoms together with the
- 30 interconnecting carbon atoms form a fused 5- or 6-membered carbocyclic or

heterocyclic ring, the fused ring systems are naphthyl, quinoliny, isoquinoliny, indolyl, indazolyl, benzimidazolyl, benzisoxazolyl, dihydrobenzofuranyl, benzoxazolyl, indanyl, benzisothiazolyl and benzothiazolyl.

- 5     12     A compound according to claim 1, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein the compound is:

(2*R*)-2-([1-([3-(4-methoxyphenyl)propyl]amino)carbonyl]cyclopentyl)methyl]-pentanoic acid (Example 16);

- 10     3-([1-([3-(4-methoxyphenyl)propyl]amino)carbonyl]cyclopentyl]propanoic acid (Example 18);

3-([1-([3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino)carbonyl]cyclopentyl]-propanoic acid (Example 21);

- 15     2-([1-([3-(4-chlorophenyl)propyl]amino)carbonyl]cyclopentyl)methyl]-4-methoxybutanoic acid (Example 15);

2-([1-([3-(4-fluorophenyl)propyl]amino)carbonyl]cyclopentyl)methyl]-4-methoxybutanoic acid (Example 4);

4-methoxy-2-([1-([3-(4-methoxyphenyl)propyl]amino)carbonyl]cyclopentyl)methyl]butanoic acid (Example 1);

- 20     2-([1-([3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino)carbonyl]cyclopentyl)methyl]-4-methoxybutanoic acid (Example 11);

(2*S*)-2-([1-([3-(4-chlorophenyl)propyl]amino)carbonyl]cyclopentyl)methyl]-4-methoxybutanoic acid (Example 22); and

- 25     (2*S*)-2-([1-([3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino)carbonyl]cyclopentyl)-methyl]-4-methoxybutanoic acid (Example 25).

- 13     (2*S*)-2-([1-([3-(4-Chlorophenyl)propyl]amino)carbonyl]cyclopentyl)methyl]-4-methoxybutanoic acid (Example 22).

30

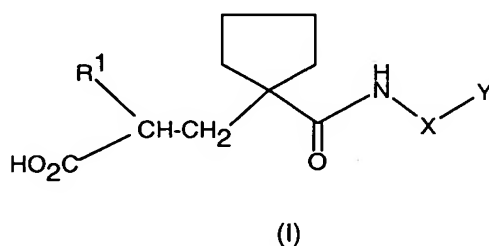
- 14     The use of a compound defined in any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, in the manufacture of a medicament for treating or preventing a condition for which a beneficial response is obtained by the inhibition of neutral endopeptidase.

35

- 15      The use according to claim 14 wherein the condition is Female Sexual Dysfunction or Male Erectile Dysfunction.
- 5      16      The use according to claim 15 wherein the condition is Female Sexual Arousal Disorder.
- 17      The use according to any one of claims 14 to 16 wherein the compound is administered systemically.
- 10      18      The use according to claim 17 wherein the compound is administered orally.
- 19      The use according to any one of claims 14 to 16 wherein the compounds are administered topically.
- 15      20      A compound defined in any one of claims 1 to 13, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, for use as a medicament.
- 20      21      A method of treating or preventing a condition for which a beneficial response is obtained by the inhibition of neutral endopeptidase in a mammal comprising treating said mammal with a therapeutically effective amount of a compound defined in any one of claims 1 to 13, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof.
- 25      22      The method of claim 21 wherein the condition is defined in claim 15 or 16.
- 23      A pharmaceutical composition including a compound defined in any one of claims 1 to 13, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof together with a pharmaceutically acceptable excipient, diluent or carrier.
- 30      24      A combination of a compound defined in any one of claims 1 to 13 and one or more active ingredients selected from the list:
- 35      a)      a PDE5 inhibitor, more preferably 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil); (6R,12aR)-2,3,6,7,12,12a-

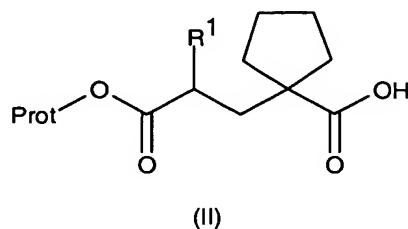
- hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) -  
 pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351); 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil); 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and pharmaceutically acceptable salts thereof;
- b) an NPY Y1 inhibitor;
- c) a dopamine agonist such as apomorphine or a selective D<sub>2</sub>, D<sub>3</sub> or D<sub>2</sub>/D<sub>3</sub>agonist such as, pramipexole and ropirinol;
- d) a melanocortin receptor agonist or modulator or melanocortin enhancer, preferably melanotan II, PT-14, PT-141;
- e) an agonist, antagonist or modulator for 5HT<sub>2C</sub>;
- f) an estrogen receptor modulator, estrogen agonists and/or estrogen antagonists, preferably raloxifene, tibolone or lasofoxifene;
- g) an androgen such as androsterone, dehydro-androsterone, testosterone, androstenedione and a synthetic androgen; and
- h) an oestrogen, such as oestradiol, oestrone, oestriol and a synthetic estrogen, such as oestrogen benzoate.

25 A process for the preparation of a compound of general formula I



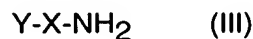
25 wherein R<sup>1</sup>, X and Y are as defined in any one of claims 1 to 13 or salts thereof comprising the steps of:

a) reacting a compound of formula II



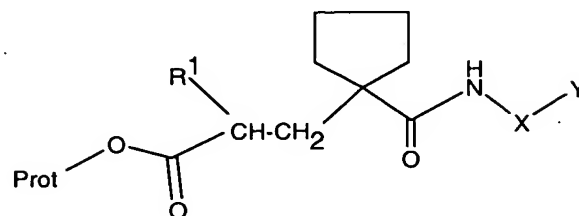
wherein Prot is a suitable protecting group, with a compound of formula

III



5

to give a compound of formula IV;



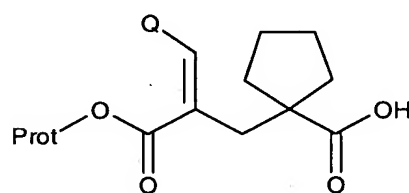
(IV)

then

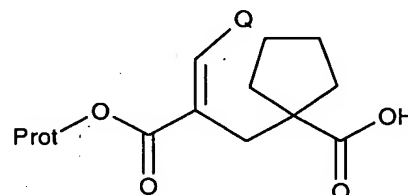
- b) reacting compound of formula IV under suitable deprotecting conditions to give the compound of formula I; then
- c) optionally forming a salt.

10

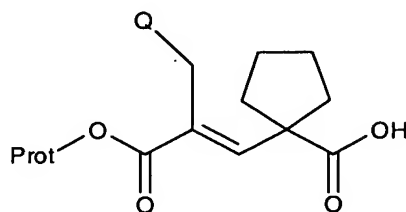
- 26 A process according to claim 25 further comprising asymmetric hydrogenation of any one of compounds of formula XI, XII or XIII



(XI)



(XII)

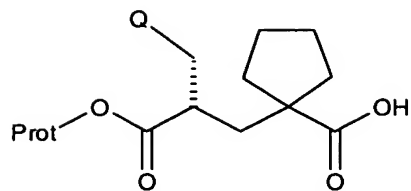


(XIII)

15

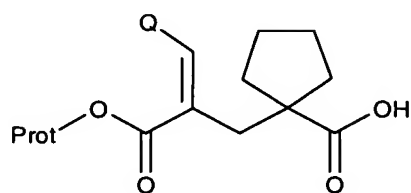
where Q is the substituent on the C<sub>1-6</sub>alkyl group defined for R<sup>1</sup> in claim 1, to give a compound of formula IIa

131

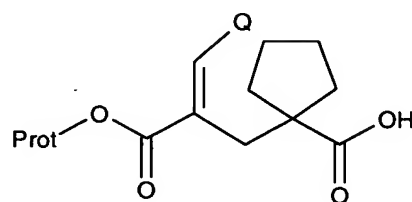


(IIa)

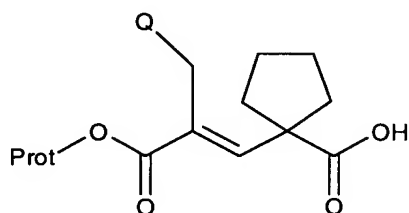
- 27 A process comprising asymmetric hydrogenation of any one of compounds of  
5 formula XI, XII or XIII



(XI)

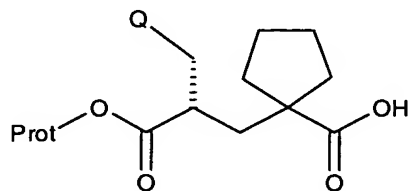


(XII)



(XIII)

where Q is the substituent on the C<sub>1-6</sub>alkyl group defined for R<sup>1</sup> in claim 1 and  
Prot is a suitable protecting group, to give a compound of formula IIa

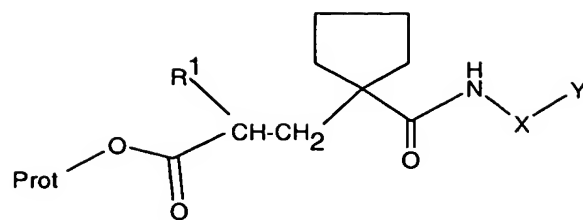


(IIa)

10

- 28 A compound of formula IV

132



(IV)

wherein  $\text{R}^1$ ,  $\text{X}$  and  $\text{Y}$  are as defined in any one of claims 1 to 13 and wherein  $\text{Prot}$  is a suitable protecting group.